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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,531	09/05/2003	Jose Remacle	035642-0103	5573

22428 7590 07/26/2007

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EXAMINER	
STEELE, AMBER D	
ART UNIT	**PAPER NUMBER**
1639	
MAIL DATE	**DELIVERY MODE**
07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,531	REMACLE ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *10-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendment to the claims received on May 16, 2007 changed the status identifiers only.

Claims 1-30 are currently pending.

Claims 1-9 are currently under consideration.

Election/Restrictions

2. Applicants elected without traverse Group I (claims 1-9) in the reply filed on May 26, 2006.

3. Applicants elected without traverse dopamine receptor 1A as the species of capture probe, human as the species of what the capture probe is derived from, dopamine receptor 1A as the species of target nucleic acid, and fluorescent label as the species of label in the replies filed on May 26, 2006 and August 21, 2006.

4. This application contains claims 10-30 drawn to inventions nonelected without traverse in the reply filed on May 26, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

5. The reference supplied in the response received on May 16, 2007 was not submitted with a proper supplemental information disclosure statement. 37 CFR 1.98(b) requires a list of all

patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list must be submitted in a separate paper." Therefore, the reference has not been considered.

Invention as Claimed

6. A method for analyzing activation pathways controlled by neurotransmitters comprising: (i) obtaining a nucleic acid from a biological sample, (ii) contacting the nucleic acid with a microarray comprising capture probes derived from the 5 major subfamilies of amine neurotransmitter receptors, under conditions allowing hybridization of complementary strands, (iii) analyzing a two dimensional pattern of data present as intensities of spots on the surface of a support of the microarray, one spot being sufficient for obtaining the information on one neurotransmitter subtype and variations thereof.

Withdrawn Objections

7. The objection to the disclosure regarding the embedded hyperlinks is withdrawn in view of the amendment to the specification received on May 16, 2007.

8. The objection to the disclosure regarding the variability of accession numbers contained in Tables 2 and 4 is withdrawn upon further consideration since the accession numbers in Tables 2 and 4 are not presently claimed.

Withdrawn Rejection

9. The rejection of claim 4, under 35 U.S.C. 112, second paragraph, as being indefinite regarding the limitations "octopamine" and “trace amines” in lines 2-3 is withdrawn due to the

"further comprising" claim language. Please note: a 35 U.S.C. 112, second paragraph (indefinite) rejection is still on record for claim 4 (see below).

Maintained Rejections

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Please note: the text of the rejections may have been altered to clarify issues raised in the arguments from the applicants.

Claim Rejections - 35 USC § 112

11. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 1 is drawn to a method for analyzing activation pathways comprising (a) obtaining a nucleic acid from a biological sample, (b) contacting the nucleic acid with a microarray comprising capture probes (sense and/or antisense; claim 6) derived from the 5 major subfamilies of amine neurotransmitter receptors, and (c) analyzing a 2-D pattern of data from the microarray. The method as claimed encompasses all known sense and antisense probes and all potential sense and antisense probes and therefore comprises a vast number of probes. The claimed method states that the probes and biological samples must be contacted under conditions that allow hybridization of complementary strands. The claimed method does not include any

structural information regarding the sense or antisense probes. In addition, antisense is commonly known in the art as either a nucleic acid sequence that interferes with protein expression or the non-coding sequence (since a definition of antisense is not provided in the specification, either interpretation could be utilized). The production of antisense probes is particularly difficult for various reasons including the necessity to choose antisense probes with weak or absent homology for other nucleic acids beside the target, perfect homology of the antisense probe does not guarantee full specificity, stability, and preferential action (e.g. ability to block protein expression) of some sequences over others. Please refer to Nicot and Pfaff Journal of Neuroscience methods 71: 45-53, 1997 (particularly pages 47-50). Therefore, one of skill in the art would not reasonably conclude that the applicants had possession of all potential probes (particularly antisense probes).

The Specification teaches the names and accession numbers for some amine neurotransmitter receptors (please refer to Tables 1-4). However, the specification does not teach a single specific probe (sense or antisense) for any of the amine neurotransmitter receptors. Furthermore, the specification does not teach which sequences would be able to define the various subtypes from the other including closely related subtypes of receptors. Moreover, the specification does not teach which sequences correlate to activation pathways of the neurotransmitters. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the entire scope of the presently claimed invention.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description'

inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of probes consisting of full-length sequences corresponding to the accession numbers in Tables 2 and 4 as disclosed by the specification, the skilled artisan cannot envision the method of claim 1 and particularly the antisense probes of present claim 6 wherein antisense may be interpreted as either the non-coding strand or a nucleic acid sequence that interferes with protein expression. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Arguments and Response

12. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (written description), for claims 1-9 were considered but are not persuasive for the following reasons.

Applicants contend that the examiner couches the rejection as if the instant claims are directed to nucleic acids *per se*, the rejection regarding antisense probes are off the mark, and one of skill in the art would recognize that as of the filing date applicants possessed methods for analyzing neurotransmitter expression.

Applicants' arguments are not convincing for the reasons of record and because the presently claimed method is dependent on having probes which can be utilized to differentiate neurotransmitter subtypes and analyze activation pathways of neurotransmitters. Thus, the probes are an intrinsic part of the method (i.e. successful outcome of the method is dependent on the probes). Please refer to Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that: "[r]egardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

The specification is silent regarding the term antisense except in claim 6. The art recognizes two distinct definitions of antisense (i.e. the non-coding strand and a nucleic acid sequence that interferes with protein expression). During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See In re Morris, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). Since the specification (except for claim 6) is silent regarding antisense, either interpretation could be utilized. See MPEP § 2111 also.

13. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 and the dependent claims thereof recite the phrase "5 major subfamilies of amine neurotransmitter receptors", which renders the claims vague and indefinite. The specification and the claims do not define the phrase so that one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

B. The term sub-subtype in claim 3 is indefinite. The term is not defined in the specification and one of skill in the art would not be able to determine the scope of the term. For example, is a sub-subtype a mutation of a naturally occurring subtype receptor? Is a sub-subtype of the receptors currently known in the art or art sub-subtypes unknown, etc.?

C. The 16 subtypes of cholinergic receptors (see claim 3) are indefinite. The specification has failed to describe or define 16 subtypes of cholinergic receptors. Cholinergic receptors are described as muscarinic and nicotinic with the muscarinic receptors further being defined as M1, M2, M3, M4, and M5. However, 16 subtypes of cholinergic receptors are not readily defined. Therefore, the 16 subtypes of cholinergic receptors are indefinite.

D. The 14 subtypes of trace amine receptors (see claim 4) are indefinite. The trace amines are defined as tyramine, b-phenylethylamine, and tryptamine in the specification and the TA1 and TA2 receptor subtypes are described. However, 14 subtypes of trace amine receptors are not readily defined. Therefore, the 14 subtypes of trace amine receptors are indefinite.

E. Claim 3 recites the limitations "dopamine", "histamine", "serotonin", "adrenergic", and "cholinergic" in lines 3-4. There is insufficient antecedent basis for the limitations in the claim.

Arguments and Response

14. Applicants' arguments directed to the rejection under 35 USC 112, second paragraph (indefinite), for claims 1-9 were considered but are not persuasive for the following reasons.

Applicants contend that the specification clearly defines all of the terms and the claims have proper antecedent basis.

Applicants' arguments are not convincing for the reasons of record and because the specification does not clearly define the terms and the claims lack antecedent basis. Applicants are respectfully reminded that while the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, while a definition of a term in the specification may be utilized to determine the scope of the term in the claim, limitations in the specification will not be incorporated into the claim.

A. Applicants state that paragraph 60 defines the five major subfamilies of amine neurotransmitter receptors as dopamine, histamine, serotonine, adrenergic, and cholinergic. Paragraph 60 of the present specification states:

"[t]he invention provides a method for simultaneously analyzing the status of different activation pathways present in the different parts of the brain of animals, which different pathways are under the control of 5 major subfamilies of the amine neurotransmitters. The method comprises the step of obtaining nucleic acids from a biological sample and contacting the nucleic acids with a micro-array, containing on specific locations thereon at least one capture probe derived from a gene encoding a receptor for a dopamine, a histamine, a serotonine, an adrenergic and a cholinergic neurotransmitter, and determining the expression profile of said receptors in the biological sample, by evaluating the two dimensional pattern of data present as intensities of spots on the surface of the micro-array, one spot being sufficient for obtaining the information on one neurotransmitter subtype."

Thus, the specification implies that dopamine, histamine, serotonine, adrenergic and cholinergic neurotransmitters are members of the amine neurotransmitter family, but does not

define that the five major subfamilies of amine neurotransmitters are (1) dopamine, (2) histamine, (3) serotonine, (4) adrenergic, and (5) cholinergic.

B. Applicants state that paragraphs 6, 64, and 81 defines sub-subtype. Excerpts from paragraphs 6, 64, and 81 state:

Paragraph 6: "...each of the subfamilies are again divided into subtypes and sometime into sub- subtypes."

Paragraph 64: "The present method and tool allows the specific determination of the expression status in one assay of at least 60% of the various subtypes and sub-subtype genes of the GPCR or LGIC receptors regulated by all amine neurotransmitters, as exemplified by the list provided in table 1. This represents for the rat, mouse and human receptors, 5 different subtypes for dopamine, 4 for histamine, 14 for serotonin, 5 for adrenergic and 16 for cholinergic and 14 for the trace amine beside some possible subtypes being commonly detected on the same capture probe."

Paragraph 81: "Receptors sub-subtypes are sometimes closely related so that the corresponding capture probes may be designed to be capable to differentiate between these closely related sub-subtypes or to recognize all of the sub- subtypes. For example a capture probe may be designed common for all subtypes Adra 2a, 2b, 2c and giving an overall analysis of the Adra 2 subtype receptors, while capture probes, distinguishing between the sub-subtypes may be designed, which are e.g. shown in table 4."

Thus, the specification does not define what sub-subtypes are or how neurotransmitters are categorized into sub-subtypes. In addition, Table 4 arbitrarily numbers the genes from 1-28 and does not categorize the genes into sub-subtypes.

C. Applicants state that Table 2 specifically identifies 16 subtypes of cholinergic receptors. However, Table 2 merely recites 16 different cholinergic receptors without indicating that each receptor is a unique subtype. In addition, the receptors in Table 2 are not limitations in the present claims.

D. Applicants state that Table 1 specifically defines 14 subtypes of trace amines. However, Table 1 merely recites 14 trace amines including octopamine without indicating that

each trace amine is a unique subtype. In addition, the trace amines in Table 1 are not limitations in the present claims.

E. Applicants state that dopamine, histamine, serotonine, adrenergic, and cholinergic have antecedent basis because they are the five major subfamilies of amine neurotransmitter receptors. This is not found persuasive because dopamine, histamine, serotonine, adrenergic, and cholinergic lack antecedent basis (please refer to section A above).

Claim Rejections - 35 USC § 102

15. Claims 1 and 5-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Kodira et al. U.S. Patent 6,890,731 filed August 4, 2000.

For present claim 1, Kodira et al. teach GPCR (G-protein coupled receptor) arrays which are utilized in methods for the development of therapeutics comprising obtaining a sample, hybridizing the sample to a nucleic acid array, and analyzing the sample (please refer to columns 1-5). In addition, Kodira et al. teach the generic GPCR superfamily and provide specific examples including dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, acetylcholine receptors, adrenaline receptors, and melatonin receptors (i.e. five major subfamilies of the amine neurotransmitter receptors; please refer to columns 2-5, 23-33).

For present claim 5, Kodira et al. teach dopamine receptors 1-5, thirteen serotonin 5-HT receptors and serotonin 5-HT3 receptor, three subtypes of adrenergic beta receptors, three subtypes of adrenergic alpha1 receptors, and three subtypes of adrenergic beta2 receptors (please refer to columns 2-5).

For present claim 6, Kodira et al. teach coding, noncoding, 5'-3', 3'-5', and antisense probes (please refer to columns 23-26 and 31).

For present claim 7, Kodira et al. teach RNA and cDNA (please refer to columns 23 and 31).

For present claim 8, Kodira et al. teach labeling nucleic acid (please refer to column 31).

For present claim 9, Kodira et al. teach fluorescent labels (please refer to column 31).

Therefore, the presently claimed invention is anticipated by the teachings of Kodira et al.

Arguments and Response

16. Applicants' arguments directed to the rejection under 35 USC 102 (e) as being anticipated by Kodira et al. for claims 1 and 5-9 were considered but are not persuasive for the following reasons.

Applicants contend that Kodira et al. does not teach utilizing an array in a method comprising contacting a nucleic acid from a sample with a microarray comprising capture probes from the 5 major subfamilies of amine neurotransmitter receptors.

Applicants' arguments are not convincing since the teachings of Kodira et al. anticipate the method of the instant claims. Kodira et al. teach GPCR (G-protein coupled receptor) arrays which are utilized in methods for the development of therapeutics comprising obtaining a sample, hybridizing the sample to a nucleic acid array, and analyzing the sample (please refer to columns 1-5). In addition, Kodira et al. teach the generic GPCR superfamily and provide specific examples including dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, acetylcholine receptors, adrenaline receptors, and melatonin receptors (i.e. subfamilies of amine neurotransmitter receptors; please

refer to columns 2-5, 23-33). For applicants' convenience, please refer to column 2, lines 32-43; column 3, lines 6-7, 19-20, 45-47, 52-55, 60-67; column 4, lines 4-27, 24, 33-34, 38-41, 44-46; column 25, lines 34-39; column 30, lines 52-67; columns 31; column 32, lines 1-53.

17. Claims 1, 3, and 5-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Williams et al. U.S. Patent 6,964,868 filed January 28, 1999.

For present claim 1, Williams et al. teach methods utilizing 7 transmembrane receptors of the rhodopsin family and G-protein coupled receptors (i.e. five major subfamilies of the amine neurotransmitter receptors) comprising providing a sample, hybridization of the sample with an array, and identifying differentially expressed genes or proteins in the sample (please refer to columns 2-5, 12-19, 23-38; Example 3).

For present claims 3 and 5, Williams et al. teach serotonin 5-hydroxytryptamine 1A-1F, 2A-2C, 4, 5A-5B, 6, and 7 (14 serotonin receptors); acetylcholine receptor (1 cholinergic receptor); muscarinic receptors M1-M5 (5 additional cholinergic receptors); adenosine receptors; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 (10 adrenergic receptors); angiotensin II receptors; bradykinin receptors; cannabinoid receptors; dopamine receptors D1-D5 (5 dopamine receptors); histamine H1 and H2 receptors (2 histamine receptors); octopamine receptor (1 octopamine); tryptamine receptor (1 trace amine); opioid receptors (i.e. five major subfamilies of the amine neurotransmitter receptors; please refer to Example 3).

For present claim 6, Williams et al. teach coding, noncoding, and antisense probes (please refer to abstract; columns 12-19, 28).

For present claim 7, Williams et al. teach RNA and cDNA (please refer to columns 7-8, 25).

For present claim 8, Williams et al. teach labeling nucleic acids (please refer to columns 7, 25-26, 32-33).

For present claim 9, Williams et al. teach fluorescent labels (please refer to columns 7, 25-26, 32-33).

Therefore, the presently claimed invention is anticipated by the teachings of Williams et al.

Arguments and Response

18. Applicants' arguments directed to the rejection under 35 USC 102 (e) as being anticipated by Williams et al. for claims 1, 3, and 5-9 were considered but are not persuasive for the following reasons.

Applicants contend that Williams et al. does not teach a method comprising contacting a nucleic acid form a sample with a microarray comprising capture probes from the five major subfamilies of amine neurotransmitter receptors.

Applicants' arguments are not convincing since the teachings of Williams et al. anticipate the method of the instant claims. Williams et al. teach methods utilizing 7 transmembrane receptors of the rhodopsin family and G-protein coupled receptors comprising providing a sample, hybridization of the sample with an array, and identifying differentially expressed genes or proteins in the sample (please refer to columns 2-5, 12-19, 23-38; Example 3). In addition, Williams et al. teach serotonin 5-hydroxytryptamine 1A-1F, 2A-2C, 4, 5A-5B, 6, and 7 (14 serotonin receptors); acetylcholine receptor (1 cholinergic receptor); muscarinic receptors M1-M5 (5 additional cholinergic receptors); adenosine receptors; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 (10 adrenergic receptors); angiotensin II receptors; bradykinin receptors;

cannabinoid receptors; dopamine receptors D1-D5 (5 dopamine receptors); histamine H1 and H2 receptors (2 histamine receptors); octopamine receptor (1 octopamine); tryptamine receptor (1 trace amine); opioid receptors (i.e. probes from five major subfamilies of amine neurotransmitter receptor; please refer to Example 3). Williams et al. also teach SEQ ID NOs: 1-5252 as probes (please refer to column 2, lines 1-4). For applicants' convenience, please refer to column 2, lines 1-45; column 3, lines 22-67; column 5, lines 1-22; column 7, lines 7-25; column 23, lines 15-24; column 24, lines 54-67; column 56, lines 12-52.

Claim Rejections - 35 USC § 103

19. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kodira et al. U.S. Patent 6,890,731 filed August 4, 2000; Borowsky et al. PNAS 98(16): 8966-8971, 2001 (June 31); Oda et al. Folia Pharmacol. Jpn. 118: 36-42, 2001 (July); Hosey The FASEB Journal 6: 845-852, 1992; and Dani Biol. Psychiatry 49: 166-174, 2001.

For present claim 1, Kodira et al. teach GPCR (G-protein coupled receptor) arrays which are utilized in methods for the development of therapeutics comprising obtaining a sample, hybridizing the sample to a nucleic acid array, and analyzing the sample (please refer to columns 1-5). In addition, Kodira et al. teach the generic GPCR superfamily and provide specific examples including dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, acetylcholine receptors, adrenaline receptors, and melatonin receptors (i.e. five major subfamilies of the amine neurotransmitter receptors; please refer to columns 2-5, 23-33).

For present claims 3 and 5, Kodira et al. teach dopamine receptors 1-5 (5 dopamine receptors), thirteen serotonin 5-HT receptors and serotonin 5-HT3 receptor (14 serotonin

receptors), three subtypes of adrenergic beta receptors, three subtypes of adrenergic alpha1 receptors, and three subtypes of adrenergic beta2 receptors for a total of 9 adrenergic receptors (please refer to columns 2-5).

For present claim 6, Kodira et al. teach coding, noncoding, 5'-3', 3'-5', and antisense probes (please refer to columns 23-26 and 31).

For present claim 7, Kodira et al. teach RNA and cDNA (please refer to columns 23 and 31).

For present claim 8, Kodira et al. teach labeling nucleic acid (please refer to column 31).

For present claim 9, Kodira et al. teach fluorescent labels (please refer to column 31).

However, Kodira et al. do not specifically teach 2 or 4 subtypes of histamine receptors. In addition, Kodira et al. do not specifically teach 4 or 16 subtypes of cholinergic receptors. Furthermore, Kodira et al. do not specifically teach 1 subtype of octopamine or 14 subtypes of trace amines.

For present claims 3 and 5, Oda et al. teach histamine receptors H1, H2, H3, and H4 are GPCRs (e.g. two histamine receptors; please refer to abstract English translation on page 42; Tables 1-2; Figures 1-2).

For present claims 3 and 5, Dani teaches nicotinic receptors are part of the acetylcholine receptor family and comprise α1-α9, β1-β4, δ, ε, and γ wherein the α and β subunits form various $\alpha\beta$ combinations (e.g. at least 16 cholinergic receptor subtypes; please refer to abstract; Introduction; Multiple Subunits Produce Nicotinic Receptor Diversity).

For present claims 3 and 5, Hosey teaches both muscarinic and nicotinic members of the cholinergic receptor family including α2βγδ, α2βδε, α2β3, and M1-M5 (e.g. at least 8 cholinergic receptor subtypes; please refer to abstract; pages 845-846).

For present claims 4-5, Borowsky et al. teach 15 G-protein coupled receptors including TA1 and TA2, one orphan receptor PNR, and octopamine that are receptors for trace amines (please refer to abstract; Introduction; Figures 1 and 3-4; Table 1; Results; Discussion).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to alter the methods for the development of therapeutics utilizing arrays comprising GPCRs, dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, and acetylcholine receptors taught by Kodira et al. with the specific receptors taught by Oda et al., Dani, Hosey, and Borowsky et al.

One having ordinary skill in the art would have been motivated to do this because Kodira et al. teach GPCRs including amine neurotransmitter receptors comprising the cholinergic receptor family, the dopamine receptor family, the serotonin receptor family, and the adrenergic receptor family. While Kodira et al. specifically teaches some members of the genus (e.g. dopamine receptors 1-5, thirteen serotonin 5-HT receptors and serotonin 5-HT3 receptor, three subtypes of adrenergic beta receptors, three subtypes of adrenergic alpha1 receptors, and three subtypes of adrenergic beta2 receptors), Kodira et al. does not teach specifically list all of the species of the genus. However, the members of the amine neurotransmitter receptor family are known in the art (e.g. 5 receptor subtypes for dopamine, 4 receptor subtypes for histamine, 14 receptor subtypes for serotonin, 5 subtypes for adrenergic receptors, 16 subtypes for cholinergic receptors, octopamine, and 14 subtypes of trace amine receptors; please refer to Oda et al., Dani,

Hosey, and Borowsky et al.). In addition, Kodira et al. teach that various GPCRs are important in various diseases including Parkinson's disease, depression, schizophrenia, Tourette's syndrome, tardive dyskinesia, Huntington's disease, OCD, panic disorder, anxiety disorder, social phobia, migraines, side effects of chemotherapy, and gastric motility disorders and thus are useful in screening for drug targets (please refer to columns 1-5 and 12). Furthermore, the addition of all known dopamine receptors, histamine receptors, serotonin receptors, adrenergic receptors, cholinergic receptors, and trace amine receptors in the array utilized in the method would be a design choice based on the desired outcome of the screening method.

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of methods for the development of therapeutics utilizing arrays comprising GPCRs, dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, and acetylcholine receptors taught by Kodira et al. with the specific receptors taught by Oda et al., Dani, Hosey, and Borowsky et al. because of the various references provided and incorporated by reference by Kodira et al. regarding how to prepare microarrays (please refer to columns 30-33).

Arguments and Response

20. Applicants' arguments directed to the rejection under 35 USC 103 (a) as being unpatentable over Kodira et al., Borowsky et al., Oda et al., Hosey, and Dani for claims 1-9 were considered but are not persuasive for the following reasons.

Applicants contend that Kodira et al., Borowsky et al., Oda et al., Hosey, and Dani do not teach utilizing an array in a method comprising contacting a nucleic acid from a sample with a microarray comprising capture probes from the 5 major subfamilies of amine neurotransmitter

receptors. In addition, applicants contend that the no reason for combining the references has been provided.

Applicants' arguments are not convincing since the teachings of Kodira et al., Borowsky et al., Oda et al., Hosey, and Dani render the method of the instant claims *prima facie* obvious. Kodira et al. teach GPCR (G-protein coupled receptor) arrays which are utilized in methods for the development of therapeutics comprising obtaining a sample, hybridizing the sample to a nucleic acid array, and analyzing the sample (please refer to columns 1-5). In addition, Kodira et al. teach the generic GPCR superfamily and provide specific examples including dopamine receptors, cholinergic receptors, muscarinic receptors, serotonin receptors, adrenergic receptors, aminergic receptors, acetylcholine receptors, adrenaline receptors, and melatonin receptors (i.e. subfamilies of amine neurotransmitter receptors; please refer to columns 2-5, 23-33). For applicants' convenience, please refer to column 2, lines 32-43; column 3, lines 6-7, 19-20, 45-47, 52-55, 60-67; column 4, lines 4-27, 24, 33-34, 38-41, 44-46; column 25, lines 34-39; column 30, lines 52-67; columns 31; column 32, lines 1-53.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Kodira et al. teach GPCRs including amine neurotransmitter receptors comprising the cholinergic receptor family, the dopamine receptor family, the serotonin receptor

family, and the adrenergic receptor family. While Kodira et al. specifically teaches some members of the genus (e.g. dopamine receptors 1-5, thirteen serotonin 5-HT receptors and serotonin 5-HT3 receptor, three subtypes of adrenergic beta receptors, three subtypes of adrenergic alpha1 receptors, and three subtypes of adrenergic beta2 receptors), Kodira et al. does not teach specifically list all of the species of the genus. However, the members of the amine neurotransmitter receptor family are known in the art (e.g. 5 receptor subtypes for dopamine, 4 receptor subtypes for histamine, 14 receptor subtypes for serotonin, 5 subtypes for adrenergic receptors, 16 subtypes for cholinergic receptors, octopamine, and 14 subtypes of trace amine receptors; please refer to Oda et al., Dani, Hosey, and Borowsky et al.). In addition, Kodira et al. teach that various GPCRs are important in various diseases including Parkinson's disease, depression, schizophrenia, Tourette's syndrome, tardive dyskinesia, Huntington's disease, OCD, panic disorder, anxiety disorder, social phobia, migraines, side effects of chemotherapy, and gastric motility disorders and thus are useful in screening for drug targets (please refer to columns 1-5 and 12). Furthermore, the addition of all known dopamine receptors, histamine receptors, serotonin receptors, adrenergic receptors, cholinergic receptors, and trace amine receptors in the array utilized in the method would be a design choice based on the desired outcome of the screening method.

21. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. U.S. Patent 6,964,868 filed January 28, 1999; Borowsky et al. PNAS 98(16): 8966-8971, 2001 (June 31); Oda et al. Folia Pharmacol. Jpn. 118: 36-42, 2001 (July); and Dani Biol. Psychiatry 49: 166-174, 2001.

For present claim 1, Williams et al. teach methods utilizing 7 transmembrane receptors of the rhodopsin family and G-protein coupled receptors (i.e. five major subfamilies of the amine neurotransmitter receptors) comprising providing a sample, hybridization of the sample with an array, and identifying differentially expressed genes or proteins in the sample (please refer to columns 2-5, 12-19, 23-38; Example 3).

For present claims 3-5, Williams et al. teach serotonin 5-hydroxytryptamine 1A-1F, 2A-2C, 4, 5A-5B, 6, and 7 (14 serotonin receptors); acetylcholine receptor (1 cholinergic receptor); muscarinic receptors M1-M5 (5 additional cholinergic receptors); adenosine receptors; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 (10 adrenergic receptors); angiotensin II receptors; bradykinin receptors; cannabinoid receptors; dopamine receptors D1-D5 (5 dopamine receptors); histamine H1 and H2 receptors (2 histamine receptors); octopamine receptor (1 octopamine); tryptamine receptor (1 trace amine); opioid receptors (i.e. five major subfamilies of the amine neurotransmitter receptors; please refer to Example 3).

For present claim 6, Williams et al. teach coding, noncoding, and antisense probes (please refer to abstract; columns 12-19, 28).

For present claim 7, Williams et al. teach RNA and cDNA (please refer to columns 7-8, 25).

For present claim 8, Williams et al. teach labeling nucleic acids (please refer to columns 7, 25-26, 32-33).

For present claim 9, Williams et al. teach fluorescent labels (please refer to columns 7, 25-26, 32-33).

However, Williams does not specifically teach 4 subtypes of histamine receptors. In addition, Williams does not specifically teach 16 subtypes of cholinergic receptors. Furthermore, Williams does not specifically teach 14 subtypes of trace amines.

For present claims 3 and 5, Oda et al. teach histamine receptors H1, H2, H3, and H4 are GPCRs (e.g. two histamine receptors; please refer to abstract English translation on page 42; Tables 1-2; Figures 1-2).

For present claims 3 and 5, Dani teaches nicotinic receptors are part of the acetylcholine receptor family and comprise α1-α9, β1-β4, δ, ε, and γ wherein the α and β subunits form various αβ combinations (e.g. at least 16 receptor subtypes; please refer to abstract; Introduction; Multiple Subunits Produce Nicotinic Receptor Diversity).

For present claims 4-5, Borowsky et al. teach 15 G-protein coupled receptors including TA1 and TA2 and one orphan receptor PNR that are receptors for trace amines (please refer to abstract; Introduction; Figures 1 and 3-4; Table 1; Results; Discussion).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the method utilizing receptors of the rhodopsin family and G-protein coupled receptors including 14 serotonin receptors; acetylcholine receptor; muscarinic receptors M1-M5; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 receptors; dopamine receptors D1-D5; histamine H1 and H2 receptors; octopamine receptor; and tryptamine (trace amine) receptor on an array to identify differentially expressed proteins and/or nucleic acids with the specific receptors taught by Oda et al., Dani, and Borowsky et al.

One having ordinary skill in the art would have been motivated to do this because Williams et al. teaches the genuses of GPCR, rhodopsin family receptors, serotonin receptors,

acetylcholine receptors, muscarinic receptors, adrenergic receptors, cholinergic receptors, dopamine receptors, histamine receptors, octopamine receptor, and tryptamine receptor. While all the known species of the various genuses were not specifically taught by Williams et al., 5 receptor subtypes for dopamine, 4 receptor subtypes for histamine, 14 receptor subtypes for serotonin, 5 subtypes for adrenergic receptors, 16 subtypes for cholinergic receptors, octopamine, and 14 subtypes of trace amine receptors are known in the art (please refer to Oda et al., Dani, Hosey, and Borowsky et al.). In addition, Williams et al. teach that the rhodopsin family and GPCRs can be utilized for chromosome mapping, tissue profiling including in cancer cells, diagnosis or prognosis of diseases, determining differential expression of proteins and/or nucleic acids (please refer to columns 25-31). Furthermore, the addition of all known dopamine receptors, histamine receptors, serotonin receptors, adrenergic receptors, cholinergic receptors, and trace amine receptors in the array utilized in the method would be a design choice based on the desired outcome of the screening method.

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method utilizing receptors of the rhodopsin family and G-protein coupled receptors including 14 serotonin receptors; acetylcholine receptor; muscarinic receptors M1-M5; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 receptors; dopamine receptors D1-D5; histamine H1 and H2 receptors; octopamine receptor; and tryptamine (trace amine) receptor on an array to identify differentially expressed proteins and/or nucleic acids with the specific receptors taught by Oda et al., Dani, and Borowsky et al. because of the various literature provided by Williams for producing microarrays (please refer to column 28).

Arguments and Response

22. Applicants' arguments directed to the rejection under 35 USC 103 (a) as being unpatentable over Williams et al., Borowsky et al., Oda et al., and Dani for claims 1-9 were considered but are not persuasive for the following reasons.

Applicants contend that Williams et al., Borowsky et al., Oda et al., and Dani do not teach a method comprising contacting a nucleic acid form a sample with a microarray comprising capture probes from the five major subfamilies of amine neurotransmitter receptors. In addition, applicants contend that the no reason for combining the references has been provided.

Applicants' arguments are not convincing since the teachings of Williams et al., Borowsky et al., Oda et al., and Dani render the method of the instant claims *prima facie* obvious. Williams et al. teach methods utilizing 7 transmembrane receptors of the rhodopsin family and G-protein coupled receptors comprising providing a sample, hybridization of the sample with an array, and identifying differentially expressed genes or proteins in the sample (please refer to columns 2-5, 12-19, 23-38; Example 3). In addition, Williams et al. teach serotonin 5-hydroxytryptamine 1A-1F, 2A-2C, 4, 5A-5B, 6, and 7 (14 serotonin receptors); acetylcholine receptor (1 cholinergic receptor); muscarinic receptors M1-M5 (5 additional cholinergic receptors); adenosine receptors; adrenergic alpha-1A-1C, alpha-2A-2D, beta-1-3 (10 adrenergic receptors); angiotensin II receptors; bradykinin receptors; cannabinoid receptors; dopamine receptors D1-D5 (5 dopamine receptors); histamine H1 and H2 receptors (2 histamine receptors); octopamine receptor (1 octopamine); tryptamine receptor (1 trace amine); opioid receptors (i.e. probes from five major subfamilies of amine neurotransmitter receptor; please

refer to Example 3). Williams et al. also teach SEQ ID NOs: 1-5252 as probes (please refer to column 2, lines 1-4). For applicants' convenience, please refer to column 2, lines 1-45; column 3, lines 22-67; column 5, lines 1-22; column 7, lines 7-25; column 23, lines 15-24; column 24, lines 54-67; column 56, lines 12-52.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Williams et al. teaches the genuses of GPCR, rhodopsin family receptors, serotonin receptors, acetylcholine receptors, muscarinic receptors, adrenergic receptors, cholinergic receptors, dopamine receptors, histamine receptors, octopamine receptor, and tryptamine receptor. While all the known species of the various genuses were not specifically taught by Williams et al., 5 receptor subtypes for dopamine, 4 receptor subtypes for histamine, 14 receptor subtypes for serotonin, 5 subtypes for adrenergic receptors, 16 subtypes for cholinergic receptors, octopamine, and 14 subtypes of trace amine receptors are known in the art (please refer to Oda et al., Dani, Hosey, and Borowsky et al.). In addition, Williams et al. teach that the rhodopsin family and GPCRs can be utilized for chromosome mapping, tissue profiling including in cancer cells, diagnosis or prognosis of diseases, determining differential expression of proteins and/or nucleic acids (please refer to columns 25-31). Furthermore, the addition of all known dopamine receptors, histamine receptors, serotonin receptors, adrenergic receptors,

cholinergic receptors, and trace amine receptors in the array utilized in the method would be a design choice based on the desired outcome of the screening method.

Conclusion

23. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
July 18, 2007

MARK L. SHIBUYA
PRIMARY EXAMINER